9/10/88

223058
RECORD #

SHAUGHNESSY NO. _____ REVIEW NO. _____

EEB REVIEW

DATE: IN _____ DATE: OUT _____

FILE OR REG. NO. 7E03489

PETITION OR EXP. NO. _____

DATE OF SUBMISSION 5/20/88

DATE RECEIVED BY EFED 5/25/88

RD REQUESTED COMPLETION DATE 9/10/88

EEB ESTIMATED COMPLETION DATE 9/10/88

RD ACTION CODE 212

TYPE OF PRODUCT(S) : I,D,H,F,N,R,S INERT

DATA ACCESSION NO(S). 406291-01, -02

PRODUCT MANAGER (NO.) Kerry Leifer (45)

PRODUCT NAME(S) CGA-154281

COMPANY NAME CIBA-GEIGY Corporation

SUBMISSION PURPOSE Submitted for review under 40 CFR 100.1001

SHAUGHNESSY NO.	CHEMICAL & FORMULATION(S)	% A.I.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Submission of CGA-154281 Data

From: James Akerman, Chief
Ecological Effects Branch
Environmental Fate and Effects Division

To: Kerry Leifer, Product Manager (45)
Registration Division

The following studies with CGA-154281 were submitted by CIBA-GEIGY Corporation for review under 40 CFR 100.1001. These studies were reviewed and categorized by EEB as follows:

Guide. Ref. #	Test Species	% ai	Test Type	Test Results	Toxicity Category	Study Status
72-1	Rainbow Trout	95.4	96-hour LC50	2.60 mg ai/L	Moderat Toxic	Suppl.
72-2	Daphnia magna	95.4	48-hour EC50	11.24 mg ai/L	Slightly Toxic	Suppl.

The attached data evaluation records will provide the necessary information concerning the repairability of studies that do not fulfill guideline requirements. If you have any questions regarding this matter, please contact Mark Roberts of my staff (557-2438).

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Accession No. 406291-01

DATA EVALUATION RECORD

1. CHEMICAL: CGA-154281

2. TEST MATERIAL: CGA-154281, 95.4% ai., a gray powder.

3. STUDY TYPE: Freshwater Fish Acute Static Test.
Species Tested: Salmo gairdneri.

4. CITATION: Drottar, K.R. 1987. Acute Toxicity of CGA-154281 to Rainbow Trout (Salmo gairdneri). Prepared by ERT, Fort Collins, Colorado. Submitted by CIBA-GEIGY Corp., Greensboro, North Carolina. Accession No. 406291-01.

5. REVIEWED BY:

Mark R. Roberts
Wildlife Biologist
EEB/EFED

Signature: Mark R. Roberts
Date: 12/5/89

6. APPROVED BY:

~~Douglas Urban~~ Ann Stavola
Supervisory Biologist
EEB/EFED

Signature: Ann Stavola
Date: 12/20/89

7. CONCLUSIONS: This study is scientifically sound but does not meet the guideline requirements for a freshwater fish acute static test. With a 96-hour LC_{50} value of 2.60 mg a.i./L, CGA-154281 is considered moderately toxic to Salmo gairdneri. The NOEL was determined to be <1.16 mg a.i./L.

8. RECOMMENDATIONS: EEB strongly recommends against the use of dechlorinated municipal water in any further aquatic testing.

9. BACKGROUND:

10. DISCUSSION OF INDIVIDUAL TESTS: N/A

11. MATERIALS AND METHODS:

A. Test Animals: Juvenile rainbow trout (Salmo gairdneri) were obtained from the Spring Creek Trout Hatchery, Lewistown, Montana. The fish were held at 10 to 20°C in test water under flowing conditions for one month before test initiation. They were fed Nelson's Sterling Cup Fish Feed daily. Two days prior to test initiation, the trout were taken off feed and

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Accession No. 406291-01

DATA EVALUATION RECORD

1. CHEMICAL: CGA-154281

2. TEST MATERIAL: CGA-154281 technical, FL Number 870211; 95.4% active ingredient; a gray powder.

3. STUDY TYPE: Freshwater Fish Acute Static Test.
Species Tested: Salmo gairdneri.

4. CITATION: Drottar, K.R. 1987. Acute Toxicity of CGA-154281 to Rainbow Trout (Salmo gairdneri). Laboratory Study No. G002-200. Prepared by ERT, Fort Collins, CO. Submitted by CIBA-GEIGY Corporation, Greensboro, NC. Accession No. 406291-01.

5. REVIEWED BY:

Prapimpan Kosalwat, Ph.D.
Staff Toxicologist
KBN Engineering and
Applied Sciences, Inc.

Signature: P. Kosalwat
Date: 8/29/88

6. APPROVED BY:

James R. Newman, Ph.D.
Project Manager/
Principal Scientist
KBN Engineering and
Applied Sciences, Inc.

Signature: J R Newman
Date: 8/30/88

Henry T. Craven, M.S.
Supervisor, EEB/HED
USEPA

Signature:
Date:

7. CONCLUSIONS: This study is scientifically sound but does not meet the guideline requirements for a freshwater fish acute static test. With a 96-hour LC50 value of 2.60 mg a.i./L, CGA-154281 is considered moderately toxic to Salmo gairdneri. The NOEL was determined to be <1.16 mg a.i./L.

8. RECOMMENDATIONS: N/A.

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held at 11-12°C. Pre-test mortality during this 48-hour period was 2.2%. The fish were 46 ± 3 mm standard length (range of 43-51 mm) and 1.4 ± 0.2 g weight.

B. Test System: The test system consisted of 38-L glass aquaria, each of which received a final volume of 35-L of test solution or control water at a depth of approximately 27.7 cm. The test was conducted at 12 to 13°C, on a photoperiod of 16-hour light and 8-hour dark.

The water used for acclimation and testing was dechlorinated (by carbon filtration), municipal water. It was characterized as follows: hardness, 22 mg/L as $CaCO_3$; and conductivity, 45 umhos/cm. The stock solution was prepared by dissolving CGA-154281 in acetone.

C. Dosage: 96-hour static LC_{50} test.

D. Design: Ten rainbow trout were randomly distributed to each test chamber. Test concentrations were not replicated. Based on a range-finding test, the fish were definitively tested at nominal concentrations of 1.3, 2.16, 3.6, 6.0, and 10.0 mg a.i./L. Two controls were conducted concurrently: a solvent control containing 500 uL/L acetone, and a dilution water control. The fish were not fed during the test and the loading density was 0.4 g/L. Test concentrations of CGA-154281 were analyzed on Days 0 and 4.

E. Statistics: The LC_{50}'s and their 95% confidence intervals were calculated by a computer program by Stephan, based on mean measured concentrations.

12. REPORTED RESULTS: Mean measured concentrations of CGA-154281 over the 96-hour test period ranged from 88 to 97% of the nominal concentrations. Test temperature was maintained at 12 to 13°C and pH ranged from 6.2 to 6.7 throughout the test. Dissolved oxygen concentrations remained at ≥ 69% of saturation throughout the 96-hour test duration.

Table 3-3 (attached) presents percent mortality of the fish in both controls and each test concentration over 96-hour period. The 24-, 48-, 72-, and 96-hour LC_{50} values are presented in Table 3-4 (attached). The no-observed-effect level (NOEL) was < 1.16 mg/L.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES: No conclusion was made by the author. The test data were reviewed by the Quality Assurance Unit of ERT to assure the standard operating procedures and protocol used in the performance of this test were followed. A statement of GLP compliance was included in the report.

14. REVIEWER'S DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Test Procedure: The test procedures were generally in accordance with the SEP, except for the following deviations:

* The test water had a slightly lower hardness than the recommended hardness of 40-48 mg/L as $CaCO_3$. In addition, dechlorinated municipal water was used as the dilution water. The use of dechlorinated water is discouraged by the SEP since removal of chlorine is rarely complete and residual chlorine can be quite toxic to aquatic organisms. In this study, there was no indication that the water had been tested for residual chlorine after passing through carbon filter. Furthermore, there were mortalities in all control and treatment groups, which might be attributed to residual chlorine.

* The age of the test fish was not stated. The report indicated that the fish were held at 10 to 20°C in test water under flowing conditions for one month prior to test initiation. The trout were taken off feed and held at 11 to 12°C only two days prior to test initiation. Therefore, they were not acclimated to study conditions for at least two weeks as recommended by the guidelines. The holding temperature went as high as 20°C, which might be too high for a coldwater fish species.

* It is not known from the report how the test temperature was maintained. According to the raw data (Appendix D), temperature monitoring was done at test initiation and each 24-hour interval. Temperature should be measured hourly if it is controlled through air temperture, or every six hours if it is controlled by a water bath.

* There was no 15- to 30-month transition period between light and dark photoperiod.

* There was no zero mortality level as recommended by the SEP.

B. Statistical Analysis: The reviewer recalculated the 96-hour LC_{50} value using EPA's TOXANAL computer program and obtained a slightly different result. The difference in result was due to Abbott's correction for control mortality.

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C. Discussion/Results: This study is scientifically sound but the reviewer suspects that some mortalities might be due to residual chlorine in the test water. A 96-hour LC_{50} value of 2.60 mg a.i./L mean measured concentration (95% C.L. = 1.94-3.46 mg/L), classifies CGA-154281 as moderately toxic to rainbow trout. The slope calculated by the probit analysis was 4.63. The NOEL was determined to be <1.16 mg a.i./L.

D. Adequacy of the Study:

(1) Classification: Supplemental.

(2) Rationale: Use of dechlorinated water as test water (see comment in Section 14.A).

(3) Repairability: Study may be upgraded to core if test water chemical characteristics incuding residual chlorine concentrations are received and judged acceptable.

15. COMPLETION OF ONE-LINER: Yes, August 22, 1988.

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4-(Dichloroacetyl)-3,4-Dihydro-3-Methyl-
2H-1,4-Benzoxazine

Page_____ is not included in this copy.

Pages 8 through 9 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

NOTE: BECAUSE THERE WAS CONTROL MORTALITY, AND NONE
OF THE LOWER CONCENTRATIONS PRODUCED ZERO MORTALITY,
THE DATA HAS BEEN SUBJECTED TO ABBOTT'S CORRECTION.

MOSALWAT CGA-154281 SALMO GAIRDNERI 6-15-83

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CONC.	NUMBER EXPOSED	NUMBER DEAD	PERCENT DEAD	BINOMIAL PROB. (PERCENT)
9.059999		9	9	100
.1953125				
5.82	9	9	100	.1953125
3.18	9	5	55.5556	50
1.93	9	2	22.2222	8.984375
1.16	9	1	11.1111	1.953125

THE BINOMIAL TEST SHOWS THAT 1.16 AND 5.82 CAN BE
USED AS STATISTICALLY SOUND CONSERVATIVE 95 PERCENT
CONFIDENCE LIMITS, BECAUSE THE ACTUAL CONFIDENCE LEVEL
ASSOCIATED WITH THESE LIMITS IS GREATER THAN 95 PERCENT.

AN APPROXIMATE LC50 FOR THIS SET OF DATA IS 2.935416

RESULTS CALCULATED USING THE MOVING AVERAGE METHOD

SPAN	G	LC50	95 PERCENT CONFIDENCE LIMITS	
3	.1954913	2.63016	1.992855	3.61039

RESULTS CALCULATED USING THE PROBIT METHOD

ITERATIONS	G	H	GOODNESS OF FIT PROBABILITY
4	.2382591	1	.6045514

SLOPE = 4.631688
95 PERCENT CONFIDENCE LIMITS = 2.370685 AND 6.892491

LC50 = 2.599075
95 PERCENT CONFIDENCE LIMITS = 1.945978 AND 3.487492

LC1 = 1.282302
95 PERCENT CONFIDENCE LIMITS = .6871851 AND [illegible]
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Accession No. 406291-02

DATA EVALUATION RECORD

1. CHEMICAL: CGA-154281

2. TEST MATERIAL: CGA-154281 Technical, 95.4% ai., a gray powder.

3. STUDY TYPE: Freshwater Invertebrate Static Acute Test. Species tested: Daphnia magna.

4. CITATION: Drotter, K. R., 1987. Acute Toxicity of CGA-154281 to the Water Flea (Daphnia magna). Prepared by ERT, Fort Collins, Colorado. Submitted by CIBA-GEIGY Corp., Greensboro, North Carolina. Accession No. 406291-02.

5. REVIEWED BY:

Mark R. Roberts
Wildlife Biologist
EEB/EFED

Signature: Mark R. Roberts
Date: 12/5/89

6. APPROVED BY:

~~Douglas Urgan~~ Ann Stavola
Supervisory Biologist
EEB/EFED

Signature: Ann Stavola
Date: 12/20/89

7. CONCLUSIONS: This study appears scientifically sound but does not fulfill the guideline requirements for a static acute freshwater invertebrate study. A valid 48-hour EC_{50} value could not be confirmed from the reported data due to the limited solubility of the ai as tested. The calculated 48-hqur EC_{50} of 11.24 mg ai/L classifies CGA-154281 as slightly toxic to Daphnia magna. The NOEL was < 4.74 mg ai/L.

8. RECOMMENDATIONS: N/A

9. BACKGROUND:

10. DISCUSSION OF INDIVIDUAL TESTS; N/A

11. MATERIALS AND METHODS:

A. Test Animals: First-instar waterfleas (Daphnia magna) were obtained from ERT's in-house cultures. Gravid females were isolated in test water at test temperature on the day prior to test initiation. At test

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Accession No. 406291-02

DATA EVALUATION RECORD

1. **CHEMICAL:** CGA-154281

2. **TEST MATERIAL:** CGA-154281 technical, FL Number 870211; 95.4% active ingredient; a gray powder.

3. **STUDY TYPE:** Freshwater Invertebrate Acute Static Test. Species Tested: Daphnia magna.

4. **CITATION:** Drottar, K.R. 1987. Acute Toxicity of CGA-154281 to the Water Flea (Daphnia magna). Laboratory Study No. G002-100. Prepared by ERT, Fort Collins, CO. Submitted by CIBA-GEIGY Corporation, Greensboro, NC. Accession No. 406291-02.

5. **REVIEWED BY:**

Prapimpan Kosalwat, Ph.D.
Staff Toxicologist
KBN Engineering and
Applied Sciences, Inc.

Signature: P. Kosalwat
Date: 8/29/88

6. **APPROVED BY:**

James R. Newman, Ph.D.
Project Manager/
Principal Scientist
KBN Engineering and
Applied Sciences, Inc.

Signature: J R Newman
Date: 8/30/88

Henry T. Craven, M.S.
Supervisor, EEB/HED
USEPA

Signature:
Date:

7. **CONCLUSIONS:** This study is scientifically sound and meets the guideline requirements for a freshwater invertebrate acute static test. With a 48-hour EC50 value of 11.47 mg a.i./L, CGA-154281 is considered slightly toxic to Daphnia magna. The NOEL was determined to be <4.74 mg a.i./L.

8. **RECOMMENDATIONS:** N/A.

initiation <24-hour old neonates were collected from this subculture for use as test organisms.

B. Test System: The test system consisted of 100 x 50 mm crystallization dishes, each of which received a final volume of 200-ml of test solution or control water at a depth of approximately 26 mm. The test was conducted at 20°C, on a photoperiod of 26-hour light and 8-hour dark.

Fresh water used for culture and testing was hard reconstituted water, with the following characteristics: hardness, 160 mg/L as $CaCO_3$; alkalinity, 107 mg/L as $CaCO_3$; and conductivity, 550 umhos/cm. The stock solution was prepared by dissolving CGA-154281 in acetone.

C. Dosage: 48-hour static EC_{50} test.

D. Design: Ten waterfleas were randomly distributed to each test chamber and all test concentrations were replicated. Based on a range-finding test, waterfleas were definitively tested at nominal concentrations of 6.48, 10.8, 18, 30, and 50 mg a.i./L. Two controls were conducted concurrently: a solvent control containing 500 uL/L acetone, and a fresh water control. The waterfleas were not fed during the test. Test concentrations of CGA-154281 were analyzed on Days 0 and 2.

E. Statistics: The EC_{50}'s and their 95% confidence intervals were calculated by a computer program by Stephan (moving average method), based on mean measured concentrations.

12. REPORTED RESULTS: Mean measured concentrations of CGA-154281 over the 48-hour period ranged from 64 to 73% of nominal concentrations. Individual measured concentrations ranged from 50-66% of nominal on day 0, and 71-81% of nominal on day 2. Test temperature was maintained at 20 to 21°C and pH was 7.8 throughout the test. The dissolved oxygen concentrations remained at $\geq$ 85% of saturation throughout the 48-hour test period.

Table 3-3 (attached) presents percent mortality of the waterfleas in both controls and each test concentration over a 48-hour period. The 24- and 48-hour EC_{50} values as calculated by the moving average method were >32.6 mg a.i./L and 11.47 mg a.i./L (95% confidence limits of 9.40-14.01 mg/L), respectively. The no-observed-effect level (NOEL) was determined to be <4.74 mg a.i./L, the lowest mean measured concentration tested.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES: No conclusion was made by the author. The test data were reviewed by the Quality Assurance Unit of ERT to assure that standard operating procedures and protocol used in the performance of this test were followed. A statement of GLP compliance was included in the report.

14. REVIEWER'S DISCUSSION:

A. Test Procedure: The test procedures were generally in accordance with the SEP, except for the following deviations:

o Hard reconstituted water, with the hardness of 160 - mg/L as $CaCO_3$, was used as the filution water in this test. The SEP recommends the use of soft water, with the hardness of 40-48 mg/L as $CaCO_3$.

o It was not known from the report how the test temperature was maintained. According to the raw data (Appendix D), temperature monitoring was done at test initiation and 24-hour intervals. Temperature should be measured hourly if it is controlled through air temperature, or every six hours if it is controlled by a water bath.

o There was no 15- to 30-minute transition period between light and dark photoperiod.

o No zero mortality level was included as recommended by the SEP.

B. Statistical Analysis: The reviewer recalculated the 48-hour EC_{50} value using EPA's TOXANAL computer program and obtained a slightly different result. Since the goodness of fit probability was greater than 0.05, the probit method was most appropriate to determine the EC_{50}.

C. Discussion/Results: There were substantial deviations between nominal and measured concentrations in this study. A film was observed in the test chamber on day 0, and measured concentrations were higher on day 2, which indicate partial insolubility and nonuniform distribution of the chemical as tested. EEB feels that because of this solubility problem, the measured concentration may have been different from that of exposure (i.e., dependent upon where the test solution was extracted for residue testing).

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The recalculated 48-hour EC_{50} value using the probit method was 11.24 mg ai/L with 95% confidence limits of 9.37 and 13.53 mg/L (attached). CGA-154281 is classified as slightly toxic to Daphnia magna with a NOEL of 4.74 mg ai/L.

Adequacy of Study:

(1) Classification: Supplemental.

(2) Rationale: The measured concentration of the ai may be unreliable due to the partial insolubility of CGA-154281 as tested. (See discussion in section 14C).

(3) Repairability: No

15. COMPLETION OF ONE LINER: Yes, November 6, 1989.

4-(Dichloroacetyl)-3,4-Dihydro-3-Methyl-
2H-1,4-Benzoxazine

Page 16 is not included in this copy.

Pages _____ through _____ are not included.

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CGA-154781

M. ROBERTS ~~VYDATE~~ DAPHNIA MAGNA 10-05-89

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CONC.	NUMBER EXPOSED	NUMBER DEAD	PERCENT DEAD	BINOMIAL PROB.(PERCENT)
32.6	20	20	100	9.536742E-05
19.15	20	18	90	2.012253E-02
11.44	20	6	30	5.765915
7.34	20	4	20	.5908966
4.74	20	3	15	.1288414

THE BINOMIAL TEST SHOWS THAT 7.34 AND 19.15 CAN BE USED AS STATISTICALLY SOUND CONSERVATIVE 95 PERCENT CONFIDENCE LIMITS, BECAUSE THE ACTUAL CONFIDENCE LEVEL ASSOCIATED WITH THESE LIMITS IS GREATER THAN 95 PERCENT.

AN APPROXIMATE LC50 FOR THIS SET OF DATA IS 13.42385

RESULTS CALCULATED USING THE MOVING AVERAGE METHOD

SPAN	G	LC50	95 PERCENT CONFIDENCE LIMITS	
4	8.643129E-02	11.40962	9.336681	13.83434

RESULTS CALCULATED USING THE PROBIT METHOD

ITERATIONS	G	H	GOODNESS OF FIT PROBABILITY
5	.1027652	1	5.562163E-02

SLOPE = 4.071986
95 PERCENT CONFIDENCE LIMITS = 2.766629 AND 5.377343

LC50 = 11.24353
95 PERCENT CONFIDENCE LIMITS = 9.367911 AND 13.52692

LC10 = 5.482967
95 PERCENT CONFIDENCE LIMITS = 3.699009 AND 6.910956

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